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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	19

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,590	TANG ET AL.	
	Examin r	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *21,22,30 and 32-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23-29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to the declaration, amendment and remarks filed on 6/26/03 in Paper Nos: 17 and 18. Claims 21-40 are pending. Claims 21, 22, 30 and 32-40 are withdrawn from as being drawn to non-elected invention. Therefore, claims 23-29 and 31 are currently being examined on the merits. Applicant has amended claims 21, 22, 25, 29 and 31.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record, which is not expressly repeated in this action, has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments and the declaration of Dr. Tod Bedilion filed 6 June 2003 under 37 C.F.R. 1.1132 have been fully considered but they are not deemed to be persuasive.

Claim Objections

5. Claims 23 and 24 are objected because they are dependent on non-elected inventions (claims 21 and 22). This objection can be overcome by rewriting claims 23 and 24 to be independent of claims 21 and 22.

Claim Rejections - 35 USC § 101, maintained

6. Claims 23-29 and 31 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for the reasons of record in Paper No: 16.

Applicant's arguments filed 26 June 2003 have been fully considered but are not deemed to be persuasive. Applicant argues that the rejection of claims 23-29 and 31 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art. These arguments are not persuasive for the following reasons.

Contrary to Applicants assertion that the novel polynucleotide codes for a polypeptide (HTMPN-22) demonstrated in the patent specification to be a member of the class of Ring3-related bromodomain proteins, whose biological functions include regulation of transcription and cell growth, the specification only teaches that HTMPN-22 is a Ring3 protein (Table 2) and recites prophetic potential uses, which include the use in diagnosis, treatment, or prevention of immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders (page 23, lines 26-30). In the absence of any functional or biological significance of this protein, there is no immediately obvious "patentable " use for it.

At page 8 of the response, applicants argue that the Examiner does not dispute that the claimed polynucleotides can be used as probes in microarrays and in gene expression monitoring systems, and allege that the Examiner "contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological function." This argument has been fully considered but is not deemed persuasive because it oversimplifies the case here. The case here is that applicants are claiming a microarray comprising nucleotides encoding SEQ ID NO: 22 or SEQ ID NO: 101, however nucleotides encoding SEQ ID NO: 22 or SEQ ID NO: 101 is the sole

characteristic by which the microarray is described. The remaining members of the microarray is not specified or described; the only recited element is nucleotide encoding SEQ ID NO: 22 or SEQ ID NO: 101, and there is no disclosed significance to SEQ ID NO: 22 itself.

While it is true that the claimed nucleic acids may be used in microarrays and in gene expression monitoring studies, the pertinent question is whether or not such use meets the criteria of 35 U.S.C. § 101 as elucidated in MPEP 2107, namely that the utility be specific, substantial and credible. The Examiner maintains that in the absence of any known biological function, or association with any disease state or condition, that the use of the claimed nucleic acids in microarrays is not specific or substantial, as one would not know of what the result was indicative; if the claimed sequences were present in a microarray, and it was shown that a nucleic acid hybridized to the claimed sequence, what information would that impart? In the absence of any knowledge of the significance of the result, the Examiner maintains that the use of the claimed nucleic acids in microarrays is not specific, as it could apply equally to any given nucleic acid, and is not substantial, because the person of ordinary skill in the art would not be apprised of the significance of the result. The Examiner notes that even if this were to be considered to be sufficient to meet the utility requirement under 35 U.S.C. § 101, the scope of the claims would not be commensurate with such use, as such use would apply only to the exact, naturally occurring sequence, and not to nucleic acids which vary from such by codon degeneracy (have different sequence, but encode the same protein) nor to nucleic acids 90% identical to the specifically disclosed sequence.

Further, even in claim 31, SEQ ID NO: 101 is not required in its entirety; claim 31 only requires 90% identity of nucleotides such which, depending upon how unique the sequence is, i.e. whether there are other related genes present in the microarray or in the sample being applied to the microarray, may not be specific for detection of SEQ ID NO: 101. With regard to "gene expression monitoring systems", the use of the claimed sequences in such systems is neither specific nor substantial, as, as argued above, such use could be argued for any naturally occurring sequence, and is not specific, nor is it substantial, as the result would not be informative. It can be argued that the use of the claimed polynucleotides in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would seem to fall under the aegis of further experimentation to determine the properties of that which is being claimed.

Note that, contrary to applicants assertion at page 8 of the response, there is no requirement being made by the Examiner that the "biological function" of the claimed polynucleotides be known to establish utility. It is noted that "biological function" may mean many things, including the ability to encode protein. The Examiner interprets "biological function" in this context to mean the actual activity of the protein encoded by the claimed nucleic acid, or the actual activity of the nucleic acid itself, if it does not encode protein. Biological function is one of the factors that might be disclosed in establishing utility, but it is not required. Note that determination of the

significance of the presence of the claimed nucleic acid in relationship to diagnosis, treatment or prevention of a developmental, cell proliferative or immunological disorder would not require any knowledge of biological function; the mere correlation of the presence of the nucleic acid, in a manner that would be found to be credible by a person of ordinary skill in the art, with the presence of a disease or condition would clearly meet the requirements of 35 U.S.C. § 101. Thus, applicant's statement that there has been a requirement made that applicants disclose the biological function of the claimed nucleic acid is incorrect.

Applicants summarize the Court's position on the utility requirement on pages 9 and 10 of the response. Applicants' review of the issue of utility, the case law that has been cited and the holding that is found in that case law is not disputed. The only point of disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Beginning at page 7 of the response, Applicant argues that the invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling, and that these uses are explained in the Bedilion Declaration. Declaration of Dr. Tod Bedilion under 37 C.F.R. § 1.132 filed in Paper No. 17(6/26/03) is insufficient to overcome the rejection of claims 23-29 and 31 because the instant specification provides general methods and no specific examples. Dr. Tod Bedilion's references to establishment of utility point to the practice of microarray technology as proposed and as addressed above. Although it is claimed that the nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO:

101 can be used as probe for microarray, there is no demonstration of the use of specific SEQ IDs for the purpose of detecting differential expression and in the use for diagnosis is provided.

At pages 12 and 13 of the response, Applicants state that "the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays", and that "Given the fact that the claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight." This argument has been fully considered but is not deemed persuasive. First, the Examiner notes that the term "highly specific" in this context indicates that the hybridization would be highly specific, that is, that the sequence could be used to detect an exactly identical sequence. However, that is not the same thing as "specific" in the context of establishing utility; *any* sequence, regardless of origin or function, can be used in such a "highly specific" manner to detect a matching sequence; however, this is the very definition of a *non-specific utility*. A non-specific utility is a utility that can be attributed to any and all members of a class of compounds. In this case, the use for "specific" hybridization or detection can be performed with any nucleic acid. Applicant's analogy to a scale is inaccurate. Using the analogy to a scale, the Examiner would argue that it is the microarray that is analogous to a scale, as a scale may be used to measure the mass of any desired object, and a microarray may be used to detect the presence of any desired nucleic acid sequence. However, the fact that a scale is useful does not confer utility on any and all objects that might be weighed using that scale, and the fact that the

microarray may have utility does not confer utility on any and all nucleic acids that might be measured using the microarray. It remains that applicants have disclosed no features or characteristics of the claimed nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 that would inform the experimenter as to what the significance of detecting that particular sequence would be. As stated above, detection of nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 under specific conditions using the claimed microarray would merely be an invitation to experiment further to determine what that result means, e.g. what significance the result has. Such an invitation to further experimentation does not meet the utility standard of 35 U.S.C. § 101.

Beginning on page 13, applicants cite several publications and argue that the "Literature review published shortly after the filing of the Tang '260 application describing the state of the art", and that such "confirm, for example, that the claimed invention is useful for differential expression analysis, regardless of how expression is regulated". The Examiner notes that these references, e.g. Rockett et al. and Lashkari et al. have not been previously cited or discussed on the record, nor have applicants in any information disclosure statement made them of record. The Rockett et al. paper (Xenobiotica 1999, 29(7): 655-691), however, supports the Examiner's assertion that the use of the claimed nucleic acids in microarrays such as that of claim 31 does not meet the requirement of being specific and substantial. In the abstract of the paper, Rockett et al. state "An important feature of the work of many molecular biologists is identifying which genes are switched on and off in a cell under different environmental

conditions or subsequent to xenobiotic challenge. **Such information has many uses, including the deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures."** (Emphasis added.). In essence, Rockett is teaching that the purpose of such "open" microarrays, wherein the function of the specific nucleic acids is unknown, as is the case for nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101, is that the results of the experiment are to be used to decipher molecular pathways, and facilitate the development of other experimental or diagnostic procedures. Such would seem to the Examiner to clearly fall under the category of use for further experimentation to determine the properties of that which is being claimed, in this case the further experimentation being to develop other procedures that would take advantage of the knowledge gained by the initial experiment, or to 'decipher' molecular pathways. Thus, it is clear from Rockett et al. that, that the use of the claimed polynucleotides in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would fall under the aegis of further experimentation to determine the properties of that which is being claimed. Similarly, the Lashkari et al. publication, by applicant's admission a pre-filing date reference that has not been previously cited, does not support applicant's assertions: While Lashkari et al. indeed teach that "amplicons", or portions of DNA amplified from the genome by PCR can be used by arraying onto glass for expression analysis, the

entire context of the article has been ignored by applicants: The very first paragraph of the paper states "This massive and increasing amount of sequence information allows the development of novel experimental approaches to identify gene function." The paragraph bridging the columns of that page starts "Experimental analysis must be performed to thoroughly understand the biological function of a gene product." The same paragraph states "it is clear that novel strategies are necessary to efficiently pursue the next phase of genome projects- whole-genome experimental analysis *to explore gene expression, gene product function, and other genome functions* (emphasis added)." Thus, Lashkari et al. are clearly teaching that sequences of unknown function or significance are used in such strategies *to learn more about the sequences themselves and the genes they represent.* The Examiner maintains that this is clearly further research of the type that is not sanctioned as fulfilling the requirements of 35 U.S.C. § 101.

Applicants argue at pages 15-17 that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, in that the facts and issues directed to each use are distinct and separable. First, Applicants argue that toxicology testing is a well-established utility, therefore, because the claimed polynucleotides could be used in this manner, the claimed invention possesses utility. Applicants are not incorrect in the conclusion that toxicology is a well-established use of polynucleotides and the polypeptides encoded. However, as indicated at page 16 of the response, all nucleic acids and genes are "useful" in toxicology testing. Therefore, this

is a utility that is nonspecific and would apply to virtually every member of a general class of materials, such as proteins or DNA. While this may be a well-established use of polynucleotides, it is not a well-established, specific, substantial and credible utility of the claimed invention. Use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. If the expression of Applicants' polynucleotide encoding SEQ ID NO: 22 or SEQ ID NO: 101 is affected by a test compound in an array for drug screening, what useful information has been gained regarding a specific and substantial utility for polynucleotide encoding SEQ ID NO: 22 or SEQ ID NO: 101 as an individually claimed entity?

Applicant's argument of the use of databases containing nucleic acid sequence information at page 18 of the response is noted, but is not deemed persuasive, as it is the nucleic acids themselves which are being claimed, and not a database, which is an informational representation.

In addition, on page 18 of the response Applicant discusses the Ocstrowski et al. (1998). This pre filing reference discusses the "Stimulation of p85/RING3 kinase in multiple organs after systemic administration of mitogens into mice". They conclude that the activation of p85/RING3 kinase by growth factors in multiple organs might reflect involvement of this enzyme in the pathogenesis of leukemias and other proliferative diseases. Although, this reference teaches a specific utility, it is not substantial because authors are only speculating on the possible involvement of this

kinase in the pathogenesis of leukemias and other proliferative diseases. In addition, it is unclear what is the homology between RING3 protein of Ocstrowski et al. and SE ID NO: 22 or the protein encoded by nucleotide sequence of SEQ ID No: 101 of the instant invention. Furthermore, it is asserted that the polypeptide encoded for by the claimed polynucleotide shares more than 57% sequence identity over 548 amino acid residues with RING3, a nuclear serine-threonine kinase. However, as previously indicated in Paper No: 16, page 4, Scott et al. (1999) teaches that the homology of a polypeptide is not a reliable indicator of the functional characteristics. In this reference on the basis of homology and the presence of a slightly modified sulfate-transporter signature sequence comprising its putative second transmembrane domain it was predicted that the pendrin protein to function as a sulfate transporter. However, experimental results indicated that it was a chloride and iodide transporter. As noted in the Applicant's response (page 20), the homology between pendrin and DRA is lower than that between HTMPN-22 and mouse RING3 (45% vs. 57%). Applicants assert based on the higher homology present between HTMPN-22 and RING3, one of ordinary skilled in the art would be reasonably convinced that HTMPN-22 is indeed a member of the RING3 related family of proteins. This is not found to be persuasive because, in order to fulfill the requirements of 35 U.S.C. § 101, it is not adequate for the invention in its current form to be part of a gene family but that it has to have specific, substantial and credible utility. Applicants current proposal would require substantial further research to identify a utility.

Furthermore, post-filing reference of French et al. (2001) shows that HTMPN-22 has 96% amino acid sequence identity to the short form of human BRD4. This is a reference that was previously cited in Paper No: 16 as an art of interest by the Office (not prior art because of the priority date), discloses that that rearrangements of the BRD4 gene is responsible for a aggressive pediatric carcinoma. In addition, Applicant also cites a post filing reference of Maruyama et al. (2002). This reference discloses that Brd4 is a member of the BET family of bromodomain proteins that includes RING3, Brd2 and that Brd4 regulates cell cycle progression. Thus, the Applicant asserts that these post-filing references confirm the identification of HTMPN-22 as a RING3 related protein and also confirms the association of this sequence with cancers. Contrary to applicant's assertion, the specification as originally filed does not specifically recite that HTMPN-22 is specifically involved neither in cancer nor in the diagnosis of this disease. Application as filed alleges several general utilities that cannot fulfill the utility requirement under 35 USC 101 because they are general and not specific (see page 23, lines 26-30 and page 37, line 25 to page 40, line 12).

At page 21 of the response, Applicants argue that a patent application can specify a utility without any knowledge as to how or why the invention has that utility. This argument is not disputed, but Applicant should note that the utility must also be specific, substantial and credible. Applicant's assertion that the claimed invention has utility in toxicology testing, drug development and disease diagnosis, as well as in regulation of proliferative tissue have all been identified as utilities which are not

specific, substantial and credible, and therefore, do not meet the requirement of 35 U.S.C. § 101.

At page 22 of the response, Applicants argue that the biological role or function of an expressed polynucleotide is not required to demonstrate utility. The Examiner agrees with this assertion; however, the Office takes issue with Applicants conclusions based upon such. While not required by any statute or rule, *if* applicants had disclosed a biological role or function of the claimed nucleic acids or the proteins encoded thereby, such *might* support a disclosed utility, such as for diagnosis or treatment of disease. However, no such role has been disclosed. This alone is not probative of lack of utility under 35 U.S.C. § 101, but is merely one of the analyses that must be made. *If* there were another specific, substantial and credible utility disclosed for the claimed nucleic acids, that would, in the absence of any knowledge of the biological function or role of the claimed nucleic acids, be sufficient to establish utility. However, that is not the case here.

At page 23, applicants argue that because the Examiner has not demonstrated that the family of polypeptides expressed by humans has any, let alone a substantial number of useless members that the examiner must conclude that there is a 'substantial likelihood' that the proteins encoded by the claimed polynucleotides are useful. This argument has been fully considered but is not deemed persuasive because this is an incorrect standard. 35 U.S.C. § 101 does not require that there be a substantial likelihood of utility, it requires that applicant have disclosed at least one specific, substantial and credible utility for that which is claimed. The fact that the

encoded protein would likely be *eventually* shown to be useful for *something* does not meet that burden. Determining what the protein would be useful for would constitute part of the act of invention. Utility must be in readily available form. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. Until some actual and specific activity can be attributed to the protein encoded by SEQ ID NO: 101 or the polynucleotides encoding it, the claimed invention is incomplete.

Applicant's argument at pages 23-24 regarding toxicology testing is redundant of earlier arguments that have been addressed above.

With regard to drug discovery and development, Applicants mention expression profiling as one use of the claimed polynucleotide. At page 24 of the response, Appellants refer to the specification regarding disease diagnosis, monitoring HTMPN-22 levels during therapeutic intervention and genomic mapping. However, a careful examination of the specification at the cited portions shows clearly that each of these purported utilities is merely use for further research and characterization of the claimed

sequences; discovery of diseases with which the sequences may be associated, or conditions under which one would want or not want to affect expression of such would constitute a part of the invention itself. All the specification as originally filed provides is a wish to know and an invitation to experiment.

With respect to Applicant's arguments at pages 24-26, the Examiner has no authority to comment regarding applicant's citation of the Written Description and Utility Guidelines, nor the statements by Mr. Kunin. However, it remains that Applicants have presented no specific and substantial utility for the claimed invention. The Examiner is not requiring a "unique" utility; if, for example, SEQ ID NO: 101 were shown to have identical expression patterns to a known cancer marker, or to be a surrogate for a cell protein of interest in toxicology, that would, indeed constitute utility. However, such is not the case here. Here, Applicants are urging that the use of the claimed nucleic acids in general methods which do not require any knowledge of the specific properties of the claimed nucleic acids is sufficient, although the results of those uses would merely be useful for further research. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or

of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement"

The instant invention has no utility and is not enabling because one cannot, following the guidance presented therein, use the claimed protein without first making a substantial inventive contribution, that is, without determining a property of the protein that would lend itself to a specific, substantial and credible use.

As Applicants recognize, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). In this case, even if utility were to be found for the nucleic acid of SEQ ID NO: 101, that the rejection of claims 23-29 and 31 under 35 U.S.C. § 112, first paragraph be affirmed on the basis that the urged utilities would apply only to the naturally occurring sequence, and therefore that enablement of the urged uses of nucleic acids encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 is not commensurate in scope with claims 22-29 and 31.

In summary, Applicant's argue that any nucleic acid isolated from a human meets the utility requirement of 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, because such nucleic acids can be used in microarrays or in gene expression studies. The

Examiner asserts that while the burden of showing utility is *not* high, that such uses do not meet that burden, as they are not specific to the particular nucleic acid being claimed, and, as supported by the references cited by appellants in the brief, such uses merely constitute use for further research. The Examiner is of the opinion that granting a patent on the nucleic acid of SEQ ID NO: 101 or to nucleotide encoding SEQ ID NO: 22 based upon the disclosure in this application would be equivalent to granting a patent on a newly discovered chemical element; all appellants have done is to isolate the nucleic acid; there is no *quid pro quo* in terms of having found and disclosed any use for the claimed nucleic acid that is based upon the particular properties of that nucleic acid. The only uses for the nucleic acid are generic ones, attributable to any naturally occurring nucleic acid sequence. The Examiner once again notes that the claims of much greater breadth than SEQ ID NO: 101 itself, and urges that even if the rejection under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is overcome, that the rejection of claims 23-29 and 31 on the basis that the utilities argued by Applicants are not commensurate in scope with the claims, and thus that enablement is not commensurate in scope with the claims. All Applicants have done is to isolate and characterize a nucleic acid sequence that occurs in nature, and seek patent protection in return for that isolation.

Claim Rejections - 35 USC § 112, first paragraph maintained

7. Rejection of claims 23-9 and 31 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and as containing subject matter which was does not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention in a manner commensurate in scope with these claims is maintained.

At page 27 of the response, Applicants argue that on pages 11 and 12 of the specification they have recited the variants having 90% sequence identity to polynucleotide encoding SEQ ID NO: 22 or nucleotide of SEQ ID NO: 101.and allege that one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO: 101 having 90% sequence identity to SEQ ID NO: 101 or encoding amino acid sequences having 90% identity to SEQ ID NO: 22. However, this argument has been fully considered but is not deemed persuasive because applicants have described only a single naturally occurring sequence, that of SEQ ID NO: 101, which encodes the predicted protein of SEQ ID NO: 22. Although, several sequences (SEQ ID NO's) have been provided there is no evidence that these sequences have at least 90% identity to nucleotides encoding SEQ ID NO: 22 or SEQ ID NO: 101. For example, there is no alignment provided that would indicate that the sequences have homology. In addition, no other naturally occurring sequences have been described as obtainable from human, nor any other animal. A breadth of 90% identity at the nucleic acid level would

reasonably be expected to encompass homologues obtained from other primate species such as macaque, rhesus, gibbon, as well as from non-primate species, such as rat or mouse, giraffe, hippo, or even frog or yeast, depending upon the evolutionary conservation of the gene in question. Applicants have provided no information or description about how conserved the gene in question is, that is, how similar the homologues from other species would be expected to be, nor have they described a single species other than the single allele (instance) of the gene as obtained from a single human. There is no description about the function of the gene nor the protein encoded thereby, such as would allow one of skill in the art to predict what portions of the disclosed sequence would be expected to be conserved. Accordingly, the mere recitation of "naturally occurring" does not obviate the issue raised with respect to written description. Similarly, with respect to claims to nucleic acids encoding proteins with 90% identity, again, no such naturally occurring variants have been disclosed, nor has any function been described for the encoded protein, nor ways in which the encoded protein might be altered while retaining that function. Further in respect to this issue, it is a nucleic acid that is being claimed; without having a written description of all naturally occurring sequences within the metes and bounds of the claims, one would not be capable of determining whether or not a given species was claimed.

On page 28, Applicants argue that variants are described, for example, at pages 15 and 23 of the specification. This argument has been fully considered but is not deemed persuasive. Page 15 of the specification merely defines what an allelic variant *is*. It does not describe even a single naturally occurring allelic variant. Similarly, at

page 23, the specification merely describes some of the things that *may* happen to cause allelic variation, i.e. to give rise to 'naturally occurring' species within the scope of the claims. However, it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single naturally occurring variant of SEQ ID NO: 101. Further, even *if* the specification had described some naturally occurring human allelic variants within the scope of the claims, such would not be commensurate in scope with the claims. This is because one of ordinary skill in the art would expect 10% variation at the nucleic acid level to read on species homologues, that is, similar sequences as isolated from different biological species. There is not a single sequence disclosed that is obtained from another biological species.

At bridging pages 27-28, Applicants argue that "one of ordinary skill in the art would recognize naturally occurring variants of SEQ ID NO: 22 having 90% identity to SEQ ID NO: 22; this is not true. One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 22, but that same person, handed a protein in a test tube, would have no way of determining whether that protein were 'naturally occurring'. The same applies to the nucleic acid of SEQ ID NO: 101.

With respect to Applicant arguments regarding sequences encoding biologically and immunologically active fragments of SEQ ID NO: 22, the Applicant is correct in that specification discloses a specific signature sequence A80-N140 of SEQ ID NO: 22. In addition, the specification also discloses nucleotide encoding SEQ ID NO: 22, which

includes sequence of SEQ ID NO: 101. However, the instant claims read on all nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is at least 90% identical to the amino acid sequence of SEQ ID NO: 22 or a nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is a biologically active fragment of the polypeptide sequence of SEQ ID NO: 22 or a nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is an immunogenic fragment of the polypeptide sequence of SEQ ID NO: 22, which the specification as failed to disclose. Contrary to Applicant's assertion, there is no description of the immunogeneic epitopes such as regions at the C-terminus or hydrophilic regions of the instant invention described in the specification at page 70, lines 2-7. The specification only teaches general computer based methods to determine regions of high immunognecity (page 70, lines 2-7). Therefore, lacking adequate written description. Similarly, Applicant has indicated the fragments listed in Table 1 can be used for hybridization. It is the position of the Office that Applicant has not provided adequate written description for the various biological activities contemplated for all the fragments contemplated in the instant claims. In addition, it appears that the Applicant was not in possession of the various fragments contemplated.

At page 29, Applicants argue that the situation in this case distinguishes from that in *Fiers* and *Lilly* because the nucleic acids in those cases were defined based on functional characteristics, and not, as here, based upon percentage identity. This argument has been fully considered but is not deemed persuasive because as a

practical matter, the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions. In this case, Applicants claims require no such conserved function. Given that, to take the claim from *Fiers* cited by Applicants, the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide" would encode proteins with *greater* than the 90% identity claimed by Applicants; the person of ordinary skill in the art would not expect to find that great an amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast interferon-beta polypeptide. Thus, the claims in both *Lilly* and *Fiers* were of *narrower* scope than the claims in question here. However, similar to the case here, both *Lilly* and *Fiers* involved disclosures of only a single sequence. Accordingly, the parallels to the instant case are clear. Thus, while recitation of structure is indeed an important factor, mere recitation of structure (90% identity to nucleic acid or the protein encoded thereby) and a product-by-process type of limitation ("naturally occurring"), without even a limitation to the biological species from which the single disclosed nucleic acid of SEQ ID NO: 101 was obtained, is insufficient to meet the written description requirement.

At page 30, Applicants argue that the claims "do not define a genus which is "highly variant"". Applicants argue that the Brenner reference states that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that the present invention is directed to

polypeptides related to the amino acid sequence of SEQ ID NO: 22 and polynucleotides related to the nucleotide sequence of SEQ ID NO: 101.

Based on analysis of Brenner et al., Applicants extrapolate the variability threshold required for establishing evolutionary homology between two sequences aligned over at least 150 residues. Brenner et al. assess that 40% identity over at least 70 residues is reliable in signifying homology between proteins. Based on these evolutionary calculations, Applicants continue to assert that the variation of the instant 90% variants of instant SEQ ID NOs: 22 and 101 is far less than what Brenner et al. had envisioned for related proteins. These arguments have not been found to be persuasive, because Brenner's calculations represent theoretical assessments and can form the basis of a hypothesis, however these calculations while providing evolutionary information do not establish the relationship of a protein biologically without a second criterion such as function, or location, or occurrence, or associated expression. Therefore, in the instant case, Brenner's calculations and applicants' analogy are well accepted as two distinct facts, but do not apply to the current grounds of rejection of lack of written description of the claimed genus described only by the chemical structure of one member without a description of how that structure correlates with the definitive properties of the genus encompassed.

To elucidate further, Applicant is misdirecting the issue. The issue here is not whether or not sequences 90% identical to SEQ ID NO: 22 or 101 would be considered to be evolutionarily related to such, but whether or not the specification as originally filed

provides an adequate written description of the 'genus'. While 90% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function. Evolutionary relatedness merely means that two entities (proteins, nucleic acid sequences, or even whole organisms) are evolutionary descendants of a common ancestor. In the process of diverging, said proteins, nucleic acids or organisms take on different structures and functions. To follow Applicant's argument to the level of organisms, it would appear that Applicants would argue that the written description of a monkey constitutes an adequate written description of a human, as the two are well known to be over 90% identical. At the protein level, there are less extreme examples; VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells, though the two are closely related. The fact that "all potential HTMPN proteins related to SEQ ID NO: 22 and polynucleotides related to SEQ ID NO: 101" as defined in the claims have a scope less than the threshold for evolutionary relatedness set forth by Brenner et al. is not relevant. What *is* relevant is that the specification as originally filed does not define a common structure or function that defines the genus claimed, and the written description is not commensurate in scope to all possible naturally occurring sequences at least 90% identical to such, which would be expected to encompass evolutionarily related, but structurally and functionally distinct, genes and proteins. It is again noted that the term "HTMPN" is defined at page 23 of the specification as being an acronym

for "human transmembrane proteins." Thus, the members of the 'class' of genes or proteins denoted as "HTMPN" are defined solely by the property of being expressed in human tissue, and there is no presumption of any shared structure, function or any other physical or functional property.

Bridging pages 31-32, Applicant argues that the art has matured considerably since the *Lilly* and *Fiers* cases. While this is true, it is not of consequence as regards this rejection for lack of adequate written description of the claimed genus. The key issue here is that Applicants have disclosed a single nucleic acid sequence, which is expected to encode a single protein. No function has been attributed to either. The claims encompass all naturally occurring nucleic acid sequences that are at least 90% identical to SEQ ID NO: 101, or all nucleic acid sequences that encode proteins 90% identical to SEQ ID NO: 22. No defining characteristics have been disclosed to identify the critical features of the genus, and no species homologues or allelic variants have been described or disclosed. Further, Applicant's own arguments of evolutionary relatedness would suggest that Applicant would argue that the disclosure of a single naturally occurring sequence is sufficient written description to entitle appellant to claim the breadth of yet-undiscovered evolutionarily related but structurally and functionally distinct nucleic acids.

7b. Rejection of claims 23-29 and 31 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Even if a patentable utility were to be established, claims 23-39 and 31 (depending upon whether the utility were predicated upon the use of the nucleic acid as a probe, or whether the utility was based upon use of the encoded protein), the specification would be found to be enabling only for an isolated polynucleotide of nucleic acids encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 and (possibly, depending upon the utility) a method of making the protein of SEQ ID NO: 101, but not to a polynucleotide sequence 90% identical to SEQ ID NO: 101 without regard to function, as recited in claim 31, nor to fragments. The specification, even if it did enable a nucleic acid having SEQ ID NO: 101 or which encodes SEQ ID NO: 22 would not be found to provide support commensurate in scope with the claims.

The specification discloses SEQ ID NO: 101, and postulates a protein having SEQ ID NO: 22 or fragment containing A80-N140 of SEQ ID NO: 22, encoded by such. No activities are ascribed to either the nucleic acid or the protein. The state of the prior art is that both sequences are novel. Although the relative level of skill in the art is high, the claims are broad, and there are no working examples or guidance or direction to allow the person of ordinary skill in the art to make and use species in a manner commensurate in scope with the claims. With particular respect to claims to nucleic acid which 'encodes' protein, if the nucleic acid were found to have utility as a hybridization probe, such would not be commensurate in scope with such claims, as the majority of such species would not be useful as hybridization probes. It is not

recognized practice in the art to alter nucleic acid sequences from their naturally occurring sequences for use as hybridization probes in any method disclosed in the specification, e.g. microarrays. Accordingly, it would require undue experimentation to determine how to use a commensurate number of species, even *if* nucleic acid of SEQ ID NO: 101 itself has utility, or *if* the protein of SEQ ID NO: 22 were found to have utility. Also, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. Thus, predicting which fragments would retain the functions of the protein is well outside the realm of routine experimentation. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences.

8. No claims are allowable.

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

JS